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Emergence of New Delhi metallo-β-lactamase type 1-producing *Enterobacteriaceae* and non-*Enterobacteriaceae*: global case detection and bacterial surveillance

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SUMMARY

Objective: A systematic review of the literature was conducted to summarize the descriptive and molecular epidemiology of human cases and surveillance reports with New Delhi metallo-β-lactamase type 1 (NDM-1)-producing bacteria reported worldwide from January 2008 through July 6, 2011.
Methods: A comprehensive literature review was conducted to identify publications of NDM-1-producing bacteria. Studies were divided into two broad categories of (1) case series and case reports of NDM-1-producing bacteria, or (2) active surveillance and environmental surveillance studies of NDM-1-producing bacteria.
Results: Sixty cases with NDM-1-producing bacteria were reported in the 3.5-year interval since the index case detection. The majority of reported cases represented colonization without evidence of infection ($n = 39$, 65%); urine was the most common specimen source for cases with infection (41.7%) and colonization (33.3%). Seventeen cases (28.3%) had NDM-1-producing bacteria at more than one body site. *Klebsiella pneumoniae* and *Escherichia coli* were the most frequent bacteria detected, and the multilocus sequence type data from 34 *E. coli* and *K. pneumoniae* clinical isolates provided an incomplete, yet heterogeneous global distribution of NDM-1-producing bacteria. The majority of cases (63.3%) had exposure to the Indian subcontinent of south central Asia, and laboratory surveillance systems, as well as an environmental survey from India, suggest a presence of environmental reservoirs for potential human infection and colonization with NDM-1-producing bacteria.
Conclusions: The majority of case reports with NDM-1-producing bacteria had presumed colonization, not infection, with one or more bacteria. The available human case reports and surveillance data suggest a global distribution of NDM-1-producing *Enterobacteriaceae* and non-*Enterobacteriaceae*.

1. Introduction

Infections with multidrug-resistant Gram-negative bacteria are of major global concern given limited therapeutic options, untoward clinical outcomes, and excess costs of care.[1,2] Heterogeneous resistance trends to cephalosporins, fluoroquinolones, and carbapenems exist among *Enterobacteriaceae* and non-*Enterobacteriaceae*, which add to the complexity of region-specific effective infection prevention and treatment strategies. Treatment of carbapenemase-resistant *Enterobacteriaceae* (CRE) now includes combination regimens of carbapenems, colistin, aminoglycosides, aztreonam, and tigecycline, as well as prolonged infusions of carbapenems.[3–11] Gram-negative bacteria with the New Delhi metallo-β-lactamase type-1 (NDM-1), produced by the $bla_{\text{NDM-1}}$ gene, utilize at least one zinc atom at the active site to facilitate hydrolysis of a broad variety of β-lactams and carbapenems.[12] The epidemiology of NDM-1 is compounded by interspecies dispersion and recognized implications for patient care, public health, antimicrobial surveillance programs, and drug development.[3,8,13–15]

Initial case detection of NDM-1 production was characterized in a clinical urinary isolate of *Klebsiella pneumoniae* from a 59-year-old man who returned to Sweden after hospitalization in India in January 2008.[16] This patient was concurrently colonized with an NDM-1-producing *Escherichia coli* in the stool.[16] Subsequently, two NDM-1-producing *E. coli* strains from 2006 were retrospectively identified in stored clinical isolates from healthcare facilities in New Delhi, India via the SENTRY Antimicrobial Surveillance Program.[17] Since 2008, NDM-1-producing bacteria have been reported via case detection, active and passive laboratory surveillance systems, national surveillance programs, and

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environmental surveillance studies.[7,17–23] The most frequent detection of NDM-1 has been in *K. pneumoniae* and *E. coli*, with global spread associated with international travel, medical tourism, and potential exposures in the Balkan region and the Indian subcontinent.[3,16,18,20,22,24–26] In Europe, a case series of subjects with NDM-1-producing *Enterobacteriaceae* has served as a template for linking clinical and laboratory case detection.[7] From an epidemiological perspective, the global burden of disease associated with NDM-1-producing pathogens remains underrepresented in the literature.[3,27] The objective of this systematic review was to characterize the global distribution of human cases and surveillance studies for NDM-1-producing bacteria for the 3.5-year period since the initial case detection.

2. Methods

2.1. Systematic literature review

A comprehensive literature review was conducted using the PubMed search engine and the following key search terms: "New Delhi Metallo-Beta-Lactamase" and "NDM-1". Search terms were limited to publications in the English language, publications in humans, and literature sources published from January 2008 (month and year of the clinical presentation of the NDM-1 index case) through July 6, 2011. Articles available through online advanced access were included and, in order to ascertain any citations that were not identified in the original literature search, relevant publications were examined for additional references to NDM-1-producing bacteria. Articles with complete text were analyzed and the relevant data from these publications were systematically collated into a tabulated format. Articles with only abstracts were included if the abstract contained sufficient information to meet the study inclusion criteria. NDM-1 publications were divided into two broad categories of either (1) case series and case reports of NDM-1-producing bacteria, or (2) active surveillance or environmental surveillance studies of NDM-1-producing bacteria. When additional information of interest for the systematic data collection was not in the publication, we attempted to contact the respective corresponding author to gather or to discern additional descriptive information for inclusion in the systematic review. Additional relevant data for 35 cases were obtained from corresponding authors of the original publications. Subsequent to the initial review of publications, we conducted a second structured literature search to assure capture of active laboratory surveillance programs and environmental surveillance studies of NDM-1-producing pathogens worldwide. This second literature review was conducted using the same search limits as the initial PubMed search with the following key search terms: "New Delhi metallo-β-lactamase", "NDM-1", "surveillance study", and "environmental study". This search did not yield any additional NDM-1 surveillance or environmental studies.

2.2. Reported cases: data collection and study definitions

A case was defined as a patient for whom at least one clinical isolate of NDM-1-producing bacteria had been isolated, confirmed, and reported in the published literature. Demographic, clinical, and microbiological data were systematically collected from the case reports and case series. The demographic data included age, gender, and geographic location at the time of the NDM-1 specimen procurement. Exposure to the Indian subcontinent of south central Asia was defined as 'yes' for residence, travel, medical care, or hospitalization, or 'no' for either lack of exposure or uncertain for exposure. The clinical data included comorbid conditions, clinical status at hospital discharge or at last follow-up, recent travel history within 1 year prior to detection of NDM-1, contact with other healthcare facilities, prior medical treatment or procedures, length of stay at the medical facility abroad, inter-country transfer, and any local transmission events with known contact of a travel-associated case. Microbiological data included the date of specimen collection, the bacterial species harboring NDM-1, specimen source(s) for both infected and colonized NDM-1 cases, and the multilocus sequence type (MLST), when available in the published literature. The MLST is a nucleotide sequence-based approach for the unambiguous characterization of bacterial isolates. Additional descriptive and microbiological data, if available, were also reviewed. Each reported case was categorized as either infection or presumed colonization. A case infection was defined as a report of NDM-1-producing bacteria in either (1) blood or another sterile body fluid specimen, or (2) clinical culture specimens from potentially non-sterile specimen sources such as the respiratory tract, wounds, urine, and other sources that were deemed to be associated with infection by the clinical investigative team. Cases with infection were further reviewed to determine if the infected case was also colonized with one or more NDM-1-producing bacteria, and if confirmed for colonization, the identified source(s) of colonization. A case of presumed colonization with NDM-1-producing bacteria was either (1) asymptomatic, (2) deemed to be colonized and without infection by the investigator/authors in either the initial report or follow-up correspondence, or (3) uncertain for infection or colonization by the original investigators, or if the author did not confirm colonization by personal communication, the case was categorized as presumed colonization. Specimens identified as urinary catheter, skin, and nose were categorically grouped as 'other' sources, and the source 'wound' included isolates from pus.

2.3. Laboratory and surveillance studies: data collection and study definitions

Identified surveillance studies for NDM-1-producing bacteria were assessed for geographic location of the patient at the time the clinical isolate was procured. Data included specimen source, date of specimen collection, number of NDM-1 isolates detected for each case, bacterial species, and when available, the MLST. The type of surveillance program, target pathogens, and denominator definitions were systematically recorded, given the variation in the laboratory detection methodologies and surveillance programs. The proportion of NDM-1-producing bacteria reported in each of these studies was contingent upon the criteria for screening restricted to either Gram-negative bacteria, *Enterobacteriaceae*, or CRE. All data were entered into Microsoft Excel for descriptive statistics and summary calculations.

3. Results

3.1. Literature review for case reports, case series, and surveillance studies

The systematic literature review yielded 94 publications with reports of NDM-1-producing bacteria published in print or online between January 2008 and July 6, 2011 and limited to humans and articles in English. Thirty-six publications were case reports or case series,[16,18,21,24,28–59] and nine publications were surveillance studies;[3,4,7,23,60–64] 49 publications were excluded. Among excluded publications was the first published case report of NDM-2, a variant form of NDM, and a report on *Acinetobacter baumannii* isolates that lacked pertinent case details.[38,65] After review of the identified publications and citations, an additional six case reports,[20,66–70] two surveillance studies,[17,71] and one Health Protection Agency report regarding carbapenem resistance and NDM-1[19] were included. These publications of NDM-1-producing

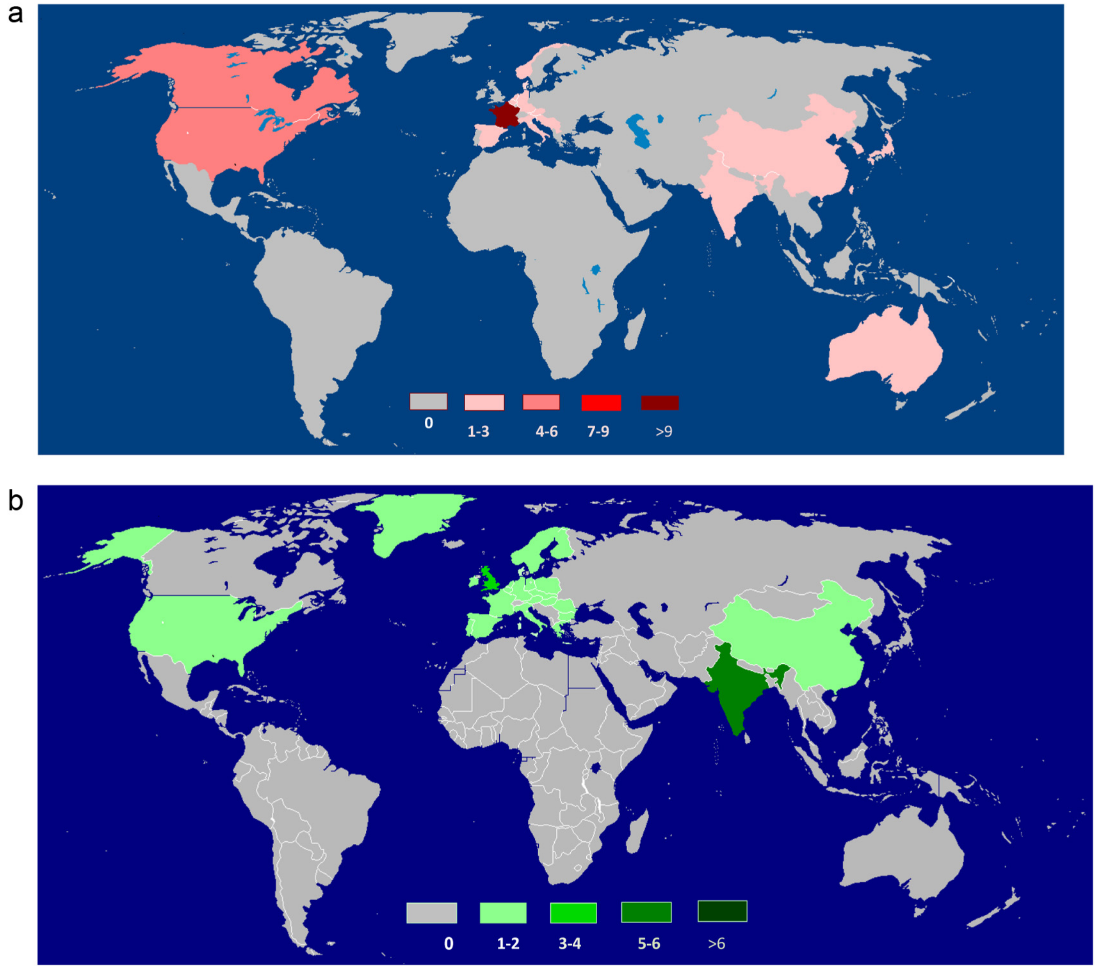

Figure 1. Two world maps illustrate (a) the international dissemination of human cases and (b) surveillance isolates with New Delhi metallo-β-lactamase (NDM-1)-producing *Enterobacteriaceae* and non-*Enterobacteriaceae*; data based on publications as of July 6, 2011.

Enterobacteriaceae and non-*Enterobacteriaceae* portray an international dissemination of case reports and series (Figure 1a) and surveillance isolates (Figure 1b).

3.2. Case cohort

The final cohort comprised 60 reported unique cases with NDM-1-producing bacteria from independent and overlapping case reports and case series.[16,18,20,21,24,28–59,66–70] Twenty-one cases (35%) were categorized as infection and 39 cases (65%) were categorized as presumed colonization with no clinical evidence of infection (Table 1). There were 29 males (48.3% of the total, with nine cases unknown for gender), most cases were adults (n = 44, 73.3% of the total; with 11 cases unknown for age), and a predominance (n = 27, 45%) of case detection in Europe (Table 1). Exposure to the Indian subcontinent of south central Asia was reported for 76.2% cases (n = 16) with NDM-1 infection versus 56.4% of cases (n = 22) with colonization. The frequency of reported case detection increased annually until 2011, with a four-fold increase in colonized cases between 2008 and 2009 and a four-fold increase in infected cases between 2009 and 2010. Crude mortality was higher among persons with infection (23.8%) versus presumed colonization (10.3%). The NDM-1-producing bacteria associated with the nine deaths were *E. coli* (n = 4), *K. pneumoniae* (n = 2), *Pseudomonas aeruginosa* (n = 2), *A. baumannii* (n = 1), and *Providencia stuartii* (n = 1); one case included detection of both NDM-1-producing *E. coli* and *K. pneumoniae*.

One or more NDM-1-producing bacteria were reported for each case, for a total of 84 NDM-1-producing bacterial isolates reported from the 60 unique cases (Table 2). The majority of reported NDM-1-producing bacteria (n = 78, 92.9%) were in the family *Enterobacteriaceae*, with *K. pneumoniae* and *E. coli* identified as the most frequently reported bacteria.[13,34,47,57,72,73] Urine was the most frequent specimen source for cases with infection (n = 10, 41.7%) and with colonization (n = 20, 33.3%). One case from Canada remained colonized and untreated with NDM-1-producing *Morganella morganii* 5 months after initial detection, and another case had *Providencia rettgeri* urine colonization 3 months after the initial microbial detection.[21] A case from Italy with enteric colonization of NDM-1-producing *E. coli* had sustained colonization 10 months after initial detection, with an interim toe infection attributed to NDM-1-producing *E. coli*.[34]

Seventeen of the 60 cases (28.3%) represented cases with NDM-1-producing bacteria at more than one body site (Table 3).[16,21,24,31,33,34,36,41,42,47,48,53,54,59] The distribution of these 17 cases included infection (n = 2), colonization (n = 5), and dual infection and colonization (n = 10).

The MLST characterization was available for 34 of the 84 (40.5%) reported NDM-1-producing bacteria (Table 4). Among the 20 *K. pneumoniae* isolates, there were seven different MLST; sequence type (ST) 14 was the most frequently detected MLST, with cases from Sweden (n = 1, the index case), Sultanate of Oman (n = 1), Singapore (n = 1), and Kenya (n = 7).[16,45,50] Among

Table 1
Descriptive characteristics of 60 reported cases with NDM-1-producing bacteria stratified by infection versus presumed colonization

Descriptive variables	Overall (n = 60)	NDM-1 infection (n = 21)	NDM-1 colonization[a] (n = 39)
Gender			
Male	29 (48.3)	12 (57.1)	17 (43.6)
Female	22 (36.7)	6 (28.6)	16 (41.0)
Unknown	9 (15.0)	3 (14.3)	6 (15.4)
Age (years)			
<18	5 (8.3)	4 (19.0)	1 (2.6)
18–65	31 (51.7)	10 (47.6)	21 (53.8)
>65	13 (21.7)	3 (14.3)	10 (25.6)
Unknown	11 (18.3)	4 (19.0)	7 (17.9)
Geographic region			
Europe	27 (45.0)	10 (47.6)	17 (43.6)
North America	12 (20.0)	4 (19.0)	8 (20.5)
Asia	11 (18.3)	6 (28.6)	5 (12.8)
Africa	7 (11.7)	0 (0.0)	7 (17.9)
Australia	3 (5.0)	1 (4.8)	2 (5.1)
Indian subcontinent exposure[b]			
Yes	38 (63.3)	16 (76.2)	22 (56.4)
No (unknown/none)	22 (36.7)	5 (23.8)	17 (43.6)
Year of case detection			
2007	3 (5.0)	1 (4.8)	2 (5.1)
2008	4 (6.7)	1 (4.8)	3 (7.7)
2009	15 (25.0)	3 (14.3)	12 (30.8)
2010	28 (46.7)	13 (61.9)	15 (38.5)
2011 (through July 6)	3 (5.0)	1 (4.8)	2 (5.1)
Uncertain[c]	7 (11.7)	2 (9.5)	5 (12.8)
Crude mortality[d]	9 (15.0)	5 (23.8)	4 (10.3)

Data are provided as number (%) unless denoted otherwise.
[a] Presumed colonization if infection not confirmed in report or by corresponding author.
[b] Residence, travel, medical care, or hospitalization to the region of south central Asia, comprising the countries of Pakistan, Bangladesh, India, Sri Lanka, and the Himalayan states of Nepal and Bhutan.
[c] Two infected cases and one colonized case detected between March 2009 and October 2010.
[d] Specimen sources associated with mortality and infection were blood ($n = 3$), urine ($n = 1$), and wound ($n = 1$). The specimen sources associated with mortality and NDM-1 colonization were urine ($n = 2$), wound ($n = 1$), and simultaneous wound and enteric colonization ($n = 1$).

the 14 *E. coli* isolates, there were seven different MLST representing cases from North America ($n = 3$), Europe ($n = 7$), Australia ($n = 1$), Japan ($n = 1$), Norway ($n = 1$), and Switzerland ($n = 1$); 71.4% ($n = 10$) had presumed case exposure in the Indian subcontinent.[31,33,34,37,41–43,46,48,52,55,58,69,70]

3.3. Laboratory and environmental surveillance for NDM-1-producing pathogens

During the 3.5-year interval since the index NDM-1 case report, 11 publications and data from the UK Health Protection Agency were reviewed for additional information related to laboratory-based or environmental surveillance for NDM-1-producing isolates (Table 5).[3,4,7,17,19,23,60–64,71] Variation in detection of NDM-1 was evident, based on the years of surveillance and the surveillance strategy by type of bacteria or by type of indication or infection among the seven publication sources from the Indian subcontinent of central Asia[3,17,23,61–64] and the six publication and data sources from the rest of world region.[3,4,7,19,60,71] In the 2006–2007 SENTRY study, 1.0% (15/1443) of *Enterobacteriaceae* were retrospectively identified as NDM-1-producing bacteria.[17] Clinical isolates with NDM-1 production were collected from New Delhi, Mumbai, and Pune; no NDM-1-producing bacteria were detected at any of the other 11 surveillance sites within India.[17] In a later study of *Enterobacteriaceae*, 1.2% of specimens from Chennai versus 13.1% from Haryana were positive for NDM-1-producing bacteria.[3] Among CRE specimens from India, 31–92% tested positive for NDM-1-producing bacteria.[3,17,61,62] An environmental surveillance study conducted in New Delhi detected NDM-1-producing bacteria in 4% ($n = 2/50$) of drinking water samples, 30% ($n = 51/171$) of seepage samples, and in 0% of the control samples, sewage effluent.[74] As of mid-March 2011 in the UK, the Health Protection Agency reported 88 isolates of NDM-1-producing CRE.[19] A comprehensive study across China found 0.03% of clinical isolates ($n = 4$ of 11 298) tested positive for NDM-1 production; all four isolates were *A. baumannii* and three of the patients were neonates.[32]

4. Discussion

The current perspective on NDM-1-producing bacteria for human and environmental health is compounded by interspecies dispersion, diverse health care practices, and varied antimicrobial surveillance programs. This systematic literature review provides three contributions to the current understanding of NDM-1-producing bacteria related to epidemiology, clinical care, and implications for international surveillance and preparedness plans. From an epidemiological perspective, the 60 cases reported in the literature over a 3.5-year period represent a heterogeneous patient population with varied multidrug-resistant phenotypes, indicative of worldwide interspecies dissemination of $bla_{\mathrm{NDM-1}}$ on plasmids.[51,72,75] NDM-1 plasmids harbor a variety of co-resistance

Table 2
Distribution of 84 NDM-1-producing *Enterobacteriaceae* ($n = 78$) and non-*Enterobacteriaceae* ($n = 6$) detected in 60 cases stratified by case infection versus colonization and by specimen source

Bacteria	Infection source ($n = 24$)				Colonization source[a] ($n = 60$)					Total
	Urine	Blood	Wound	Resp[b]	Urine	Stool	Resp[b]	Wound	Other[c]	
Klebsiella pneumoniae	5	1	1	2	13	8	4	2	4[d]	40
Escherichia coli	4	3	5	-	2	9	4	1	-	28
Providencia spp.	-	1	-	-	2	-	-	-	-	3
Citrobacter freundii	1	-	-	-	-	-	-	-	-	1
Morganella morganii	-	-	-	-	1	1	-	1	-	3
Enterobacter cloacae	-	-	-	-	1	-	-	1	-	2
Proteus mirabilis	-	-	-	-	-	1	-	-	-	1
Acinetobacter baumannii	-	1	-	-	-	-	1	1	1	4
Pseudomonas aeruginosa	-	-	-	-	1	-	-	1	-	2
Total	10	6	6	2	20	19	9	7	5	84

[a] Presumed colonization if infection not confirmed in report or by corresponding author.
[b] Resp = respiratory specimen of sputum, bronchoalveolar lavage, or other.
[c] Other = skin, nose, or urinary catheter.
[d] Source unknown for one case with *Klebsiella pneumoniae* presumed colonization.

Table 3
Descriptive case categorization of 17 reported cases with NDM-1-producing bacteria located at more than one body site and stratified as case with infection or colonization with one or two different NDM-1-producing bacteria[a]

Case	Gram-negative bacteria and infection type	Ref.
Single bacterial pathogen[b]		
Infected	*E. coli* urosepsis (blood and urine)	53
	E. coli infection (inguinal, perineum, and scrotal wounds)	59
Infected and colonized	*E. coli* blood infection and *E. coli* respiratory tract colonization	24
	K. pneumoniae abdominal wound infection and *K. pneumoniae* enteric and throat colonization	59
	A. baumannii endovascular infection and *A. baumannii* colonization (skin, tracheal secretions, and wound)	36
	K. pneumoniae RTI and *K. pneumoniae* nasal colonization	41
	K. pneumoniae UTI and *K. pneumoniae* enteric colonization	54
	E. coli toe infection and *E. coli* enteric colonization	34
	E. coli blood infection and *E. coli* urine and sputum colonization	33
Colonized	*E. coli* breast tumor colonization and enteric colonization	46
	M. morganii urine and enteric colonization	21
	K. pneumoniae decubiti and enteric colonization	59
Two different bacterial pathogens[b]		
Infected and colonized	*K. pneumoniae* UTI and *E. coli* enteric colonization	48
	K. pneumoniae UTI and *E. coli* enteric colonization	16
	K. pneumoniae UTI and *E. coli* and *K. pneumoniae* enteric colonization	42
Colonized	*M. morganii* wound and *E. cloacae* pus colonization	31
	K. pneumoniae respiratory colonization and *E. coli* enteric colonization	31

RTI, respiratory tract infection; UTI, urinary tract infection.
[a] Presumed colonization if infection not confirmed in publication or by corresponding author.
[b] NDM-1-producing bacterial pathogen reported in publication or by corresponding author.

determinants, including β-lactamase genes, quinolone resistance genes, and 16S rRNA methylase genes.[75] How diverse sequence types in bacteria contribute to the dissemination of $bla_{\text{NDM-1}}$ remains a source of ongoing investigation. The MLST data for *E. coli* and *K. pneumoniae* provide an incomplete, yet heterogeneous global distribution of NDM-1-producing *Enterobacteriaceae*, which suggests a non-clonal pattern of dissemination (Table 4). A recent, noteworthy study from a military hospital in Pakistan, published after our systematic review end-date, reported enteric prevalence rates for NDM-1-producing bacteria of 27.1% for inpatients and 13.8% for outpatients.[73] Another recent investigation of NDM-1-producing carbapenemases in *K. pneumoniae* from India, Sweden, and the USA, reported that the most frequently detected MLST sequence type was ST14, a finding consistent with what we identified for *K. pneumoniae* (Table 4).[76] Notably, the investigators have suggested that ST14 and ST11 are likely to be important in the ongoing dissemination of $bla_{\text{NDM-1}}$.[76] These data, together with environmental surveillance data (Table 5), suggest that there is a

Table 4
Distribution of multilocus sequence types (MLST) reported in 31 cases with clinical isolates of NDM-1-producing *Klebsiella pneumoniae* ($n = 20$) and NDM-1-producing *Escherichia coli* ($n = 14$)[a]

Bacteria and MLST sequence type (ST)	No.	Geographic region of isolate detection and presumed case exposure (n)	Detection by year/quarter (Q)	Ref.
K. pneumoniae, $n = 20$				
ST14	10	Sweden and India (1)	2008 Q1	16
		Sultanate of Oman and India (1)	2009 Q1	45
		Kenya and North America (7)	2007 Q2–2009 Q1	50
		Singapore and Bangladesh (1)	2010 Q1	39
ST147	4	Australia and India (1)	2010	54
		Canada and India (1)	2010 Q3	56
		Switzerland and India (1)	2009–2010	48
		France and Iraq (1)	2010 Q4	49
ST11	2	Norway and India (1)	2010 Q2	53
		Singapore and India (1)	2010 Q1	39
ST15	1	Belgium and Montenegro (1)	2010	31
ST16	1	Canada and India (1)	2010 Q1	42
ST25	1	Switzerland and North America (1)	2009–2010	48
ST340	1	Sultanate of Oman and North America (1)	2009 Q3	45
E. coli, $n = 14$				
ST101	4	Germany and India (1)	2009 Q4	69
		Canada and India (1)	2010	42
		Belgium and Pakistan (1)	2010	31
		Australia and Bangladesh (1)	Not available	70
ST405	3	Italy and North America (2)	2009 Q3	34
		Canada and India (1)	2010 Q1	42
ST131	2	France and India (1)	2009 Q2	46
		USA and India (1)	2010 Q2	37, 43
ST410	2	Switzerland and North America (1)	2009–2010	48
		Norway and India (1)	2010 Q1	53
ST38	1	Japan and India (1)	2009 Q2	33, 58
ST782	1	Belgium and Montenegro (1)	2010	31
ST156	1	Spain and India (1)	Not available	55

[a] Total greater than 100% as some cases had more than one clinical isolate sequenced.[31,41,48]

Table 5
Laboratory and environmental surveillance studies reporting detection of NDM-1-producing bacteria from the Indian subcontinent of south central Asia ($n=7$) and the rest of world regions ($n=6$)[a]

City, study years (Ref.)	Source specimen[b] (n)	NDM-1 (n)	Bacteria
Geographic region: Indian subcontinent of south central Asia[c]			
14 cities/SENTRY, 2006–2007 (17)	*Enterobacteriaceae* (1443) Carbapenem-resistant *Enterobacteriaceae* (CRE) (39) Carbapenemase producers (26)	15[d]	*Escherichia coli* (6); *Enterobacter spp* (3); *Klebsiella pneumoniae* (6)
Northeast tertiary hospital, August 2009 (63)	Surgical site infection (15) *Enterobacteriaceae* (11)	3[e]	*E. coli*; *K. pneumoniae*; *Enterobacter cloacae*
	Vascular site infection (8) *Enterobacteriaceae* (2)	1[e]	
Mumbai tertiary hospital, August–November 2009 (62)	CRE (24)	22	*Klebsiella spp* (10); *E. coli* (9); *Enterobacter spp* (2); *Morganella morganii* (1)
Chennai, through 2009 (3)	*Enterobacteriaceae* (3521) CRE (141)	44[f]	*E. coli* (19); *K. pneumoniae* (14); *E. cloacae* (7); *Proteus spp* (2); *Citrobacter freundii* (1); *Klebsiella oxytoca* (1)
Haryana, through 2009 (3)	*Enterobacteriaceae* (198) CRE (47)	26	*K. pneumoniae* (26)
Mumbai, through 2009 (3)	-	32	
Varanasi/NA (3)	-	13	
Guwahat/NA (3)	-	3	
Pakistan/multi-city, through 2009 (3)	-	25; in eight cities	
Mumbai tertiary center, 2009–2010 (61)	Carbapenem-resistant Gram-negative bacilli (310) *Enterobacteriaceae* (57)	49	*Klebsiella spp* (28); *E. coli* (13); *Enterobacter spp* (5); *M. morganii* (2); *Citrobacter spp* (1)
North India tertiary referral hospital and outpatient departments, February– July 2010 (64)	780 consecutive isolates (*E. coli*, *K. pneumoniae*, *Citrobacter spp*, *Enterobacter aerogenes*, *P. mirabilis*, *M. morganii*) 64 metallo-β-lactamase producers	54[g]	*E. coli* (30); *K. pneumoniae* (12); *Citrobacter spp* (12)
New Delhi, September–October 2010 (23)	Drinking water samples (50)	2	*C. freundii*; *E. coli; K. pneumoniae; Shigella boydii*; *Vibrio cholera*; *Aeromonas caviae*
	Seepage samples (171)	51	
	Effluent samples (70)	0	
Geographic region: rest of world			
UK, referrals to the ARMRL, through 2009 (3)	*Enterobacteriaceae* (NA) Carbapenemase-producers (73)	37[h]	*K. pneumoniae* (21); *E. coli* (7); *Enterobacter spp* (5); *C. freundii* (2); *M. morganii* (1); *Providencia spp* (1)
29 European Union member states, Iceland, and Norway, 2008–October 2010 (7)	CRE and non-*Enterobacteriaceae* producing NDM-1 (cases, not isolates)	87[i] cases; speciation for 67 isolates	*K. pneumoniae* (31); *E. coli* (16); *Enterobacter spp* (4); *C. freundii* (3); *M. morganii* (2); *Proteus mirabilis* (1); *Acinetobacter baumannii* (10)
Europe, Asia, North America, Latin America, the South Pacific and the Middle East, 2009 (4)	Ertapenem non-susceptible *Enterobacteriaceae* from IAI (235) 1+ carbapenemase gene (66)	33;[j] only in isolates from India	*K. pneumoniae* (18); *E. coli* (8); *E. cloacae* (5); *Providencia rettgeri* (1); *M. morganii* (1)
UK, 2008–March 2011 (19)	*Enterobacteriaceae* confirmed for NDM-1	88	-
France, February 2004–April 2011 (71)	Cases reported to the French Institute for Public Health Surveillance	9 cases[k]	*K. pneumoniae* (3); *E. coli* (3); *C. freundii* (1); *P. mirabilis* (1)[k]
China—multiple cities across the country, January 2009–September 2010 (60)	Sequential isolates of Gram-negative bacilli (*A. baumannii*, *P. aeruginosa*, *E. coli*, *K. pneumoniae*) screened for NDM-1 (11 298)	4[l]	*A. baumannii* (4)

ARMRL, Antibiotic Resistance Monitoring and Reference Laboratory; IAI, intra-abdominal infection; NA, not available.
[a] Duplicative reporting of NDM-1 isolates possible; Kumarasamy et al. included surveillance data for south central Asia and the rest of world regions, and is therefore counted twice.[3]
[b] Source specimen column provides details on the underlying population of isolates tested for NDM-1; in many instances the source population narrowed before testing for NDM-1 occurred, which is demonstrated with multiple rows per study location.
[c] Pakistan, Bangladesh, India, Sri Lanka, and the Himalayan states of Nepal and Bhutan.
[d] Specimen source: skin and skin structure infection ($n=7$), bloodstream infection (BSI; $n=5$), and respiratory tract infection ($n=3$); MLST performed only for *E. coli* with ST101 ($n=4$) and ST167 ($n=2$).
[e] Specimen source: surgical site infection and peripheral vascular access site infections.
[f] Specimen source: urinary tract infection, pneumonia, and BSI.
[g] Specimen source: urine ($n=23$), endotracheal tube ($n=13$), pus ($n=9$), umbilical cord tip ($n=2$), tissue ($n=2$), blood ($n=2$), catheter tip ($n=1$), sputum ($n=1$), and Foley catheter tip ($n=1$).
[h] Specimen source from 29 patients: urine ($n=15$), blood ($n=3$), sputum ($n=2$), other ($n=6$), and unknown ($n=3$).
[i] NDM-1 patients (not isolates) with one or more isolates of *Enterobacteriaceae*.
[j] MLST performed in *K. pneumoniae* and *E. coli* only; *K. pneumoniae* typing ST147 ($n=9$), ST231 ($n=1$), ST11 ($n=1$), ST101 ($n=1$), ST340 ($n=1$), ST391 ($n=1$), ST14 ($n=1$), ST20 ($n=1$), ST572 ($n=1$), and ST571 ($n=1$); *E. coli* typing ST88 ($n=4$), ST471 ($n=1$), ST2 ($n=1$), ST44 ($n=1$), and ST501 ($n=1$).
[k] 9 cases from 7 episodes (episode defined as either a sporadic case or >1 case related by an identified chain of transmission); 8 pathogens were reported for these 7 episodes.
[l] Specimen source: sputum ($n=2$), blood ($n=1$), and secretion ($n=1$).

significant colonization burden of NDM-1-producing bacteria in some geographic regions that far exceeds current estimates of case infections.

From a clinical perspective, our systematic review provides a selective, yet in-depth summary of 60 reported human cases. The majority of cases (65%) represented colonization without evidence of infection, with some cases informative for long-term, asymptomatic colonization. These case presentations have implications for individual patients, healthcare institutions, and global surveillance. Notably, case detection requires astute clinical care combined with laboratory detection methods linked to well-coordinated reporting systems. Prompt case detection facilitates isolation of patients which, in turn, will optimize low colonization pressure for NDM-1-producing bacteria in healthcare institutions. Colonization pressure has been identified as an independent risk factor for acquisition of vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, *P. aeruginosa*, and *Clostridium difficile* in defined geographic units over the past 15 years.[77–81] In healthcare settings with source patients infected or colonized with NDM-1-producing bacteria, infection prevention control strategies and attention to colonization pressure will be key factors in minimizing the spread of $bla_{\mathrm{NDM\text{-}1}}$ plasmids in defined geographic units.

The third notable contribution of this review pertains to current global surveillance and international preparedness plans. Recent reports and editorial commentaries suggest the need for a coordinated international monitoring system along with a global preparedness plan should an outbreak or endemicity of NDM-1-producing bacterial infections occur.[9,13,15,39,72,82–84] Current surveillance systems are limited given the lack of standardized detection methods for carbapenemases, distinction between NDM-1 infection and colonization, and data on potential non-human reservoirs of NDM-1 such as the animal food chain.[13] Detection and surveillance of carbapenemase-producing *Enterobacteriaceae* and non-*Enterobacteriaceae* have become important for both the selection of appropriate antimicrobial therapy and implementation of infection control measures. As carbapenemase production cannot be inferred from a standard antimicrobial resistance profile, criteria are needed to help determine which isolates should be suspected and screened for carbapenemase production and to determine whether phenotypic or genotypic tests should be adapted for the confirmation of carbapenem resistance.[13] The collective findings from this systematic review of human case reports, laboratory surveillance programs, and the environmental survey portray a complex array of microbial factors and a global antimicrobial armamentarium that has identifiable gaps for effective treatment paradigms.

We readily acknowledge several limitations associated with this systematic review. First, incident cases with NDM-1-producing bacteria were likely underestimated given that systematic mandatory reporting of CRE and other highly-resistant *Enterobacteriaceae* did not exist during the study period. Second, ascertainment bias in information and measurement, as well as reporting biases, were inherent in the study design given the recognized gaps in available information, lack of standardized microbial diagnostics, and resources available to characterize NDM-1-producing bacteria in resource-limited settings and in all geographic regions. Third, the association between exposure within the Indian subcontinent and NDM-1-producing bacteria may or may not be overestimated, as publication bias may be bidirectional and patients who reported exposure to the Indian subcontinent were perhaps more likely to be screened for NDM-1-producing bacteria. Fourth, the maps that portray the location of publications for cases and surveillance studies of NDM-1-producing bacteria (Figure 1) likely underestimate global spread. Nonetheless, they provide a comparative benchmark with the reports of *K. pneumoniae* carbapenemases (KPC) and other evolving carbapenemases.[85] The first KPC was detected in a 1996 clinical isolate from North Carolina and there are now nine KPC variants.[85,86] Fifth, as defined by our study and reported in our results, this review was restricted to NDM-1-producing bacteria and did not include subsequently characterized variant forms of NDM. Lastly, it is likely that case infections relative to case colonization are underestimated based on our study definitions and follow-up on clinical case data with corresponding authors. Nonetheless, epidemiological studies utilizing well-established base populations and a clear and standardized disease definition are optimal methods for estimating the incidence and prevalence of infections and colonization with NDM-1-producing bacteria.

This systematic literature review summarizes the epidemiology, clinical cases, and surveillance studies of NDM-1-producing bacteria over the 3.5-year interval since the initial characterization of a urinary isolate of NDM-1-producing *K. pneumoniae*. A global distribution of NDM-1-producing *Enterobacteriaceae* and non-*Enterobacteriaceae* is evident, linked to both human infection and colonization, and there are recognized implications for antimicrobial drug development programs and population health.[3,8,13–15] Overall, the findings in this systematic review, compounded by the complexity of the genetic plasticity of $bla_{\mathrm{NDM\text{-}1}}$, support the need for astute clinical case recognition, reliable laboratory detection methods, secure infection control practices, and well-integrated surveillance systems.

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References

1. Giske CG, Monnet DL, Cars O, Carmeli Y, on behalf of ReAct-Action on Antibiotic Resistance. Clinical and economic impact of common multidrug-resistant Gram-negative bacilli. *Antimicrob Agents Chemother* 2008;**52**:813–21.
2. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. *Nat Med* 2004;**10**:S122–9.
3. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis* 2010;**10**:597–602.
4. Lascols C, Hackel M, Marshall SH, Hujer AM, Bouchillon S, Badal R, et al. Increasing prevalence and dissemination of NDM-1 metallo-(-lactamase in India: data from the SMART study (2009). *J Antimicrob Chemother* 2011;**66**:1992–7.
5. Livermore DM, Warner M, Mushtaq S, Doumith M, Zhang J, Woodford N. What remains against carbapenem-resistant *Enterobacteriaceae*? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline. *Int J Antimicrob Agents* 2011;**37**:415–9.
6. Nordmann P, Poirel L, Toleman MA, Walsh TR. Does broad-spectrum beta-lactam resistance due to NDM-1 herald the end of the antibiotic era for treatment of infections caused by Gram-negative bacteria? *J Antimicrob Chemother* 2011;**66**:689–92.
7. Struelens MJ, Monnet DL, Magiorakos AP, Santos OF, Giesecke J, The European NDM-1 Survey Participants. New Delhi metallo-beta-lactamase 1-producing *Enterobacteriaceae*: emergence and response in Europe. *Euro Surveill* 2010;**15**:19716.
8. Walsh TR. Emerging carbapenemases: a global perspective. *Int J Antimicrob Agents* 2010;**36**(Suppl 3):S8–14.

9. Walsh TR, Toleman MA. The new medical challenge: Why NDM-1? Why Indian? *Expert Rev Anti Infect Ther* 2011;**9**:137–41.
10. Apisarnthanarak A, Mundy LM. Use of high-dose 4-hour infusion of doripenem in combination with fosfomycin, for treatment of carbapenem-resistant *Pseudomonas aeruginosa* pneumonia. *Clin Infect Dis* 2010;**51**:1352–4.
11. Apisarnthanarak A, Mundy LM. Carbapenem resistant *Pseudomonas aeruginosa* pneumonia with intermediate minimum inhibitory concentrations to doripenem: combination therapy with high dose 4-hour infusion of doripenem plus fosfomycin versus intravenous colistin plus fosfomycin. *Int J Antimicrob Agents* 2012;**39**:271–2.
12. Marra A. NDM-1: a local clone emerges with worldwide aspirations. *Future Microbiol* 2011;**6**:137–41.
13. Miriagou V, Cornaglia G, Edelstein M, Galani I, Giske CG, Gniadkowski M, et al. Acquired carbapenemases in Gram-negative bacterial pathogens: detection and surveillance issues. *Clin Microbiol Infect* 2010;**16**:112–22.
14. Queenan AM, Bush K. Carbapenemases: the versatile beta-lactamases. *Clin Microbiol Rev* 2007;**20**:440–58.
15. Walsh TR, Toleman MA, Poirel L, Nordmann P. Metallo-β-lactamases: the quiet before the storm? *Clin Microbiol Rev* 2005;**18**:306–25.
16. Yong D, Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, Walsh TR. Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. *Antimicrob Agents Chemother* 2009;**53**:5046–54.
17. Castanheira M, Deshpande LM, Mathai D, Bell JM, Jones RN, Mendes RE. Early dissemination of NDM-1- and OXA-181-producing *Enterobacteriaceae* in Indian hospitals: report from the SENTRY Antimicrobial Surveillance Program, 2006–2007. *Antimicrob Agents Chemother* 2011;**55**:1274–8.
18. Hammerum AM, Toleman MA, Hansen F, Kristensen B, Lester CH, Walsh TR, Fuursted K. Global spread of New Delhi metallo-beta-lactamase 1. *Lancet Infect Dis* 2010;**10**:829–30.
19. Health Protection Agency. Epidemiological data (carbapenem resistance and NDM-1). London, UK: Health Protection Agency; 2011. Available at: http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/CarbapenemResistance/EpidemiologicalData/ (accessed July 2011).
20. Jovcic B, Lepsanovic Z, Suljagic V, Rackov G, Begovic J, Topisirovic L, Kojic M. Emergence of NDM-1 metallo-β-lactamase in *Pseudomonas aeruginosa* clinical isolates from Serbia. *Antimicrob Agents Chemother* 2011;**55**:3929–31.
21. Kus JV, Tadros M, Simor A, Low DE, McGeer AJ, Willey BM, et al. New Delhi metallo-β-lactamase-1: local acquisition in Ontario, Canada, and challenges in detection. *CMAJ* 2011;**183**:1257–61.
22. Livermore DM, Walsh TR, Toleman M, Woodford N. Balkan NDM-1: escape or transplant? *Lancet Infect Dis* 2011;**11**:164.
23. Walsh TR, Weeks J, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. *Lancet Infect Dis* 2011;**11**:355–62.
24. Chan HL, Poon LM, Chan SG, Teo JW. The perils of medical tourism: NDM-1-positive *Escherichia coli* causing febrile neutropenia in a medical tourist. *Singapore Med J* 2011;**52**:299–302.
25. Pillai DR, McGeer A, Low DE. New Delhi metallo-beta-lactamase-1 in *Enterobacteriaceae*: emerging resistance. *CMAJ* 2011;**183**:59–64.
26. Tängdén T, Cars O, Melhus A, Löwdin E. Foreign travel is a major risk factor for colonization with *Escherichia coli* producing CTX-M-type extended-spectrum β-lactamases: a prospective study with Swedish volunteers. *Antimicrob Agents Chemother* 2010;**54**:3564–8.
27. Hawkey PM, Jones AM. The changing epidemiology of resistance. *J Antimicrob Chemother* 2009;**64**:i3–10.
28. Centers for Disease Control and Prevention. Detection of *Enterobacteriaceae* isolates carrying metallo-beta-lactamase—United States, 2010. *MMWR Morb Mortal Wkly Rep* 2010;**59**:750.
29. Birgy A, Doit C, Mariani-Kurkdjian P, Genel N, Faye A, Arlet G, Bingen E. Early detection of colonization by VIM-1-producing *Klebsiella pneumoniae* and NDM-1-producing *Escherichia coli* in two children returning to France. *J Clin Microbiol* 2011;**49**:3085–7.
30. Bogaerts P, Verroken A, Jans B, Denis O, Glupczynski Y. Global spread of New Delhi metallo-beta-lactamase 1. *Lancet Infect Dis* 2010;**10**:831–2.
31. Bogaerts P, Bouchahrouf W, de Castro RR, Deplano A, Berhin C, Piérard D, et al. Emergence of NDM-1-producing *Enterobacteriaceae* in Belgium. *Antimicrob Agents Chemother* 2011;**55**:3036–8.
32. Chen TL, Fung CP, Lee SD. Spontaneous eradication of a NDM-1 positive *Klebsiella pneumoniae* that colonized the intestine of an asymptomatic carrier. *J Chin Med Assoc* 2011;**74**:104.
33. Chihara S, Okuzumi K, Yamamoto Y, Oikawa S, Hishinuma A. First case of New Delhi metallo-beta-lactamase 1-producing *Escherichia coli* infection in Japan. *Clin Infect Dis* 2011;**52**:153–4.
34. D'Andrea MM, Venturelli C, Giani T, Arena F, Conte V, Bresciani P, et al. Persistent carriage and infection by multidrug-resistant *Escherichia coli* ST405 producing NDM-1 carbapenemase: report on the first Italian cases. *J Clin Microbiol* 2011;**49**:2755–8.
35. Diene SM, Bruder N, Raoult D, Rolain JM. Real-time PCR assay allows detection of the New Delhi metallo-beta-lactamase (NDM-1)-encoding gene in France. *Int J Antimicrob Agents* 2011;**37**:544–6.
36. Göttig S, Pfeifer Y, Wichelhaus TA, Zacharowski K, Bingold T, Averhoff B, et al. Global spread of New Delhi metallo-beta-lactamase 1. *Lancet Infect Dis* 2010;**10**:828–9.
37. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant *Enterobacteriaceae*: epidemiology and prevention. *Clin Infect Dis* 2011;**53**:60–7.
38. Kaase M, Nordmann P, Wichelhaus TA, Gatermann SG, Bonnin RA, Poirel L. NDM-2 carbapenemase in *Acinetobacter baumannii* from Egypt. *J Antimicrob Chemother* 2011;**66**:1260–2.
39. Koh TH, Khoo CT, Wijaya L, Leong HN, Lo YL, Lim LC, Koh TY. Global spread of New Delhi metallo-beta-lactamase 1. *Lancet Infect Dis* 2010;**10**:828.
40. Leverstein-Van Hall MA, Stuart JC, Voets GM, Versteeg D, Tersmette T, Fluit AC. Global spread of New Delhi metallo-beta-lactamase 1. *Lancet Infect Dis* 2010;**10**:830–1.
41. Mochon AB, Garner OB, Hindler JA, Krogstad P, Ward KW, Lewinski MA, et al. New Delhi metallo-beta-lactamase (NDM-1)-producing *Klebsiella pneumoniae*: case report and laboratory detection strategies. *J Clin Microbiol* 2011;**49**:1667–70.
42. Mulvey MR, Grant JM, Plewes K, Roscoe D, Boyd DA. New Delhi metallo-beta-lactamase in *Klebsiella pneumoniae* and *Escherichia coli*, Canada. *Emerg Infect Dis* 2011;**17**:103–6.
43. Peirano G, Schreckenberger PC, Pitout JD. Characteristics of NDM-1-producing *Escherichia coli* isolates that belong to the successful and virulent clone ST131. *Antimicrob Agents Chemother* 2011;**55**:2986–8.
44. Peirano G, Ahmed-Bentley J, Woodford N, Pitout JD. New Delhi metallo-beta-lactamase from traveler returning to Canada. *Emerg Infect Dis* 2011;**17**:242–4.
45. Poirel L, Al Maskari Z, Al Rashdi F, Bernabeu S, Nordmann P. NDM-1-producing *Klebsiella pneumoniae* isolated in the Sultanate of Oman. *J Antimicrob Chemother* 2011;**66**:304–6.
46. Poirel L, Hombrouck-Alet C, Freneaux C, Bernabeu S, Nordmann P. Global spread of New Delhi metallo-beta-lactamase 1. *Lancet Infect Dis* 2010;**10**:832.
47. Poirel L, Hervé V, Hombrouck-Alet C, Nordmann P. Long-term carriage of NDM-1-producing *Escherichia coli*. *J Antimicrob Chemother* 2011;**66**:2185–6.
48. Poirel L, Schrenzel J, Cherkaoui A, Bernabeu S, Renzi G, Nordmann P. Molecular analysis of NDM-1-producing enterobacterial isolates from Geneva, Switzerland. *J Antimicrob Chemother* 2011;**66**:1730–3.
49. Poirel L, Fortineau N, Nordmann P. International transfer of NDM-1-producing *Klebsiella pneumoniae* from Iraq to France. *Antimicrob Agents Chemother* 2011;**55**:1821–2.
50. Poirel L, Revathi G, Bernabeu S, Nordmann P. Detection of NDM-1-producing *Klebsiella pneumoniae* in Kenya. *Antimicrob Agents Chemother* 2011;**55**:934–6.
51. Poirel L, Ros A, Carricajo A, Berthelot P, Pozzetto B, Bernabeu S, Nordmann P. Extremely drug-resistant *Citrobacter freundii* isolate producing NDM-1 and other carbapenemases identified in a patient returning from India. *Antimicrob Agents Chemother* 2011;**55**:447–8.
52. Roy S, Viswanathan R, Singh AK, Das P, Basu S. Sepsis in neonates due to imipenem-resistant *Klebsiella pneumoniae* producing NDM-1 in India. *J Antimicrob Chemother* 2011;**66**:1411–3.
53. Samuelsen Ø, Thilesen CM, Heggelund L, Vada AN, Kümmel A, Sundsfjord A. Identification of NDM-1-producing *Enterobacteriaceae* in Norway. *J Antimicrob Chemother* 2011;**66**:670–2.
54. Sidjabat H, Nimmo GR, Walsh TR, Binotto E, Htin A, Hayashi Y, et al. Carbapenem resistance in *Klebsiella pneumoniae* due to the New Delhi metallo-beta-lactamase. *Clin Infect Dis* 2011;**52**:481–4.
55. Solé M, Pitart C, Roca I, Fàbrega A, Salvador P, Muñoz L, et al. First description of an *Escherichia coli* strain producing NDM-1 carbapenemase in Spain. *Antimicrob Agents Chemother* 2011;**55**:4402–4.
56. Tijet N, Alexander DC, Richardson D, Lastovetska O, Low DE, Patel SN, Melano RG. New Delhi metallo-beta-lactamase, Ontario, Canada. *Emerg Infect Dis* 2011;**17**:306–7.
57. Wu HS, Chen TL, Chen IC, Huang MS, Wang FD, Fung CP, Lee SD. First identification of a patient colonized with *Klebsiella pneumoniae* carrying blaNDM-1 in Taiwan. *J Chin Med Assoc* 2010;**73**:596–8.
58. Yamamoto T, Takano T, Iwao Y, Hishinuma A. Emergence of NDM-1-positive capsulated *Escherichia coli* with high resistance to serum killing in Japan. *J Infect Chemother* 2011;**17**:435–9.
59. Zarfel G, Hoenigl M, Leitner E, Salzer HJ, Feierl G, Masoud L, et al. Emergence of New Delhi metallo-beta-lactamase, Austria. *Emerg Infect Dis* 2011;**17**:129–30.
60. Chen Y, Zhou Z, Jiang Y, Yu Y. Emergence of NDM-1-producing *Acinetobacter baumannii* in China. *J Antimicrob Chemother* 2011;**66**:1255–9.
61. Deshpande P, Shetty A, Kapadia F, Hedge A, Soman R, Rodrigues C. New Delhi metallo 1: have carbapenems met their doom? *Clin Infect Dis* 2010;**51**:1222.
62. Deshpande P, Rodrigues C, Shetty A, Kapadia F, Hedge A, Soman R. New Delhi metallo-beta lactamase (NDM-1) in *Enterobacteriaceae*: treatment options with carbapenems compromised. *J Assoc Physicians India* 2010;**58**:147–9.
63. Sarma JB, Bhattacharya PK, Kalita D, Rajbangshi M. Multidrug-resistant *Enterobacteriaceae* including metallo-beta-lactamase producers are predominant pathogens of healthcare-associated infections in an Indian teaching hospital. *Indian J Med Microbiol* 2011;**29**:22–7.
64. Seema K, Ranjan SM, Upadhyay S, Bhattacharjee A. Dissemination of the New Delhi metallo-beta-lactamase-1 (NDM-1) among *Enterobacteriaceae* in a tertiary referral hospital in north India. *J Antimicrob Chemother* 2011;**66**:1646–7.
65. Karthikeyan K, Thirunarayan M, Krishnan P. Coexistence of blaOXA-23 with blaNDM-1 and armA in clinical isolates of *Acinetobacter baumannii* from India. *J Antimicrob Chemother* 2010;**65**:2253–4.
66. Centers for Disease Control and Prevention. Notes from the field: detection of blaNDM-1 carbapenem resistance in a clinical isolate of *Providencia stuartii* in a U.S./Coalition medical facility—Afghanistan, 2011. *MMWR Morb Mortal Wkly Rep* 2011;**60**:756–7.

67. Chu YW, Tung VWN, Cheung TKM, Chu MY, Cheng N, Lai C, et al. Carbapenemases in enterobacteria, Hong Kong, China, 2009. *Emerg Infect Dis* 2011;**17**:130–2.
68. Fernando G ATP, Collignon PJ, Bell JM. A risk for returned travellers: the ''post-antibiotic era''. *Med J Aust* 2010;**193**:59.
69. Pfeifer Y, Witte W, Holfelder M, Busch J, Nordmann P, Poirel L. NDM-1-producing *Escherichia coli* in Germany. *Antimicrob Agents Chemother* 2011;**55**:1318–9.
70. Poirel L, Lagrutta E, Taylor P, Pham J, Nordmann P. Emergence of metallo-beta-lactamase NDM-1-producing multidrug-resistant *Escherichia coli* in Australia. *Antimicrob Agents Chemother* 2010;**54**:4914–6.
71. Vaux S, Carbonne A, Thiolet JM, Jarlier V, Colgnard B, RAISIN and Expert Laboratories Group. Emergence of carbapenemase-producing *Enterobacteriaceae* in France, 2004–2011. *Euro Surveill* 2011;**16**:19880.
72. Bonomo RA. New Delhi metallo-beta-lactamase and multidrug resistance: a global SOS? *Clin Infect Dis* 2011;**52**:485–7.
73. Perry JD, Naqvi SH, Mirza IA, Alizai SA, Hussain A, Ghirardi S, et al. Prevalence of faecal carriage of *Enterobacteriaceae* with NDM-1 carbapenemase at military hospitals in Pakistan, and evaluation of two chromogenic media. *J Antimicrob Chemother* 2011;**66**:2288–94.
74. Coque TM, Baquero F, Canton R. Increasing prevalence of ESBL-producing *Enterobacteriaceae* in Europe. *Euro Surveill* 2008;**13**:19044.
75. Poirel L, Dortet L, Bernabeu S, Nordmann P. Genetic features of *bla*NDM-1-positive *Enterobacteriaceae*. *Antimicrob Agents Chemother* 2011;**55**:5403–7.
76. Giske CG, Fröding I, Hasan CH, Turlej-Rogacka A, Toleman M, Livermore D, et al. Diverse sequence types of *Klebsiella pneumoniae* contribute to the dissemination of $bla_{\mathrm{NDM\text{-}1}}$ in India, Sweden, and the United Kingdom. *Antimicrob Agents Chemother* 2012;**56**:2735–8.
77. Bonten MJ, Slaughter S, Ambergen AW, Hayden MK, van Voorhis J, Nathan C, Weinstein RA. The role of ''colonization pressure'' in the spread of vancomycin-resistant enterococci: an important infection control variable. *Arch Intern Med* 1998;**158**:1127–32.
78. Bonten MJM, Bergmans CJJ, Speijer H, Stobberingh EE. Characteristics of polyclonal endemicity of *Pseudomonas aeruginosa* colonization in intensive care units. *Am J Respir Crit Care Med* 1999;**16**:1212–9.
79. Lawrence SJ, Puzniak LA, Shadel BN, Gillespie KN, Kollef MH, Mundy LM. *Clostridium difficile* in the intensive care units: epidemiology costs and colonization pressure. *Infect Control Hosp Epidemiol* 2007;**28**:123–30.
80. Lucet JC, Paoletti X, Lolom I, Paugam-Burtz C, Trouillet JL, Timsit JF, et al. Successful long-term program for controlling methicillin-resistant *Staphylococcus aureus* in intensive care units. *Intensive Care Med* 2005;**31**:1051–7.
81. Williams VR, Callery S, Vearncombe M, Simor AE. The role of colonization pressure in nosocomial transmission of methicillin-resistant *Staphylococcus aureus*. *Am J Infect Control* 2009;**37**:106–10.
82. Kanungo R. New Delhi metallo-beta-lactamase 1: is there a need to worry? *Indian J Med Microbiol* 2010;**28**:275–6.
83. Rolain JM, Parola P, Cornaglia G. New Delhi metallo-beta-lactamase (NDM-1): towards a new pandemia? *Clin Microbiol Infect* 2010;**16**:1699–701.
84. Shahid M. Environmental dissemination of NDM-1: time to act sensibly. *Lancet Infect Dis* 2011;**11**:334–5.
85. Oelschlaeger P, Ai N, DuPrez KT, Welsh WJ, Toney JH. Evolving carbapenemases: can medicinal chemists advance one step ahead of the coming storm? *J Med Chem* 2010;**53**:3013–27.
86. Yigit H, Queenam AM, Anderson GJ, Domenech-Sanchez A, Biddle JW, Steward CD, et al. Novel carbapenem-hydrolyzing β-lactamase, KPC-1, from a carbapenem-resistant strain of Klebsiella pneumoniae. *Antimicrob Agents Chemother* 2001;**45**:1151–61.